CASE REPORTS

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Fat Overload From 10 Percent Soybean Oil Emulsion in a Marrow Transplant Recipient

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MARROW TRANSPLANTATION is a complex procedure that frequently requires intensive supportive care, including nutritional support. The Seattle transplant group routinely places a large-bore right atrial catheter for prophylactic administration of total parenteral nutrition including the use of a 10 percent soybean emulsion (Intralipid, manufactured by Cutter Medical Division of Cutter Laboratories, Berkeley, California 94710).[1] We describe our first case of the so-called fat-overload syndrome from Intralipid administration.

Report of a Case

A 25-year-old man was admitted to the Fred Hutchinson Cancer Research Center in July 1979 for allogeneic marrow transplantation for severe aplastic anemia. The presumed cause of the aplastic anemia was viral hepatitis, though toxic hepatitis could not be excluded. The hepatitis B surface antigen was negative and a test for surface antibody was positive. At the time of admission, leukocytes numbered 300 per cu mm, the platelet count was 68,000 per cu mm following transfusion and the hematocrit was 22.4 percent. The serum bilirubin was 2.4 mg per dl, the alkaline phosphatase was 131 IU per liter (N, 13 to 39), the serum aspartate aminotransferase (formerly serum glutamic oxaloacetic transaminase, SGOT) was 58 IU per liter (N, 0 to 41), the lactate dehydrogenase (LDH) was 175 IU per liter (N, 60 to 220) and the serum creatinine was 1.2 mg per dl (N, 1 to 2). Blood cultures were positive for *Escherichia coli*. A right atrial catheter was placed on the day of admission and total parenteral nutrition was begun the following day with 25 percent dextrose, a 4.25 percent crystalline amino acid solution (FreAmine II) and 500 ml of Intralipid per day.[1] He was treated with broad spectrum antibiotics. Marrow transplantation was carried out a week later (day 0) as previously described.[2]

The first month posttransplantation was relatively uneventful, with clearing of the Gram-negative septicemia and return of the results of liver function tests to the normal range, except for an LDH between 160 and 500 IU per liter. On day 18 a skin biopsy was found to be positive for graft-versus-host disease. This syndrome remained clinically mild without specific therapy until day 29 when the administration of methylprednisolone, 160 mg a day, was begun because of abdominal pain and diarrhea presumed to be due to graft-versus-host disease. At this time the serum bilirubin was 1.0 mg per dl, the alkaline phosphatase was 217, SGOT 27 and LDH 236 IU per liter and the serum creatinine was 0.8 mg per dl. Despite steroid therapy the diffuse rash progressed, the diarrhea increased to 2 liters per day and the serum bilirubin rose to 5.0 mg per dl, with an SGOT of 126 and alkaline phosphatase of 459 IU per liter. These changes were attributed to graft-versus-host disease, and on day 40 the patient was started on the administration of horse antithymocyte globulin (Upjohn) at a dosage of 15 mg per kg of body weight per day through day 53 and every other day until day 61.

On day 42 the quantity of Intralipid was increased to 1 liter a day. At this time the patient was critically ill with increasing liver dysfunction, ascites and large volumes of bloody diarrhea (2 to 3 liters a day). He had adequate marrow function.

Concomitant with antithymocyte globulin ad-

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ministration, the rash and liver disease lessened but not the diarrhea. By day 53 the serum bilirubin was 0.8 mg per dl, the alkaline phosphatase was 188, SGOT 21 and the LDH 196 IU per liter. Amphotericin B administration was begun on day 69 because of persistent fever and cultures of the blood were positive on day 70 for *Candida tropicalis*. On day 64 the LDH rose to 618 IU per liter and continued to rise, reaching a peak of 4,390 on day 74. At the same time the SGOT rose from 219 to 310 IU per liter and the bilirubin from 0.9 to 3.4 mg per dl. By day 75 the serum creatinine was 2.9 mg per dl and the blood urea nitrogen (BUN) was 76 mg per dl (N, 8 to 25), with a good urine volume.

On day 71 his serum was noted to be lipemic and burgundy colored, and administration of Intralipid was discontinued. On day 73 the serum was still lipemic, hemolysis was still present and the serum triglyceride level was 483 mg per dl (N, 40 to 150).

LDH fractionation showed pronounced increases in all fractions. Serum creatine phosphokinase, amylase, calcium and phosphorus were all normal. Coagulation studies showed a prolonged partial thromboplastin time, thrombin time and reptilase time, with a normal fibrinogen and prothrombin time. Peripheral blood smears showed many nucleated red blood cells and vacuolated polymorphonuclear leukocytes. An oil red 0 stain of the peripheral blood smear was positive for neutral fat both within the vacuoles of granulocytes and in the plasma. The patient's red blood cells showed burr cell formation (see Figure 1). An osmotic fragility curve was abnormal, with increased hemolysis at sodium chloride concentrations greater than 0.6 percent, and 20 percent hemolyzed cells were present at 0.8 percent normal saline solution. On day 72 the patient had abdominal pain and shortness of breath. Oxygen pressure (Po_2) with the patient breathing room air was 47.5 mm of mercury and carbon dioxide pressure (Pco_2) was 33.1 mm of mercury. The patient was placed on supplemental oxygen. His chest film was unchanged.

At this point it was felt that he had iatrogenic fat overload leading to respiratory insufficiency, hemolytic anemia and acute renal failure.

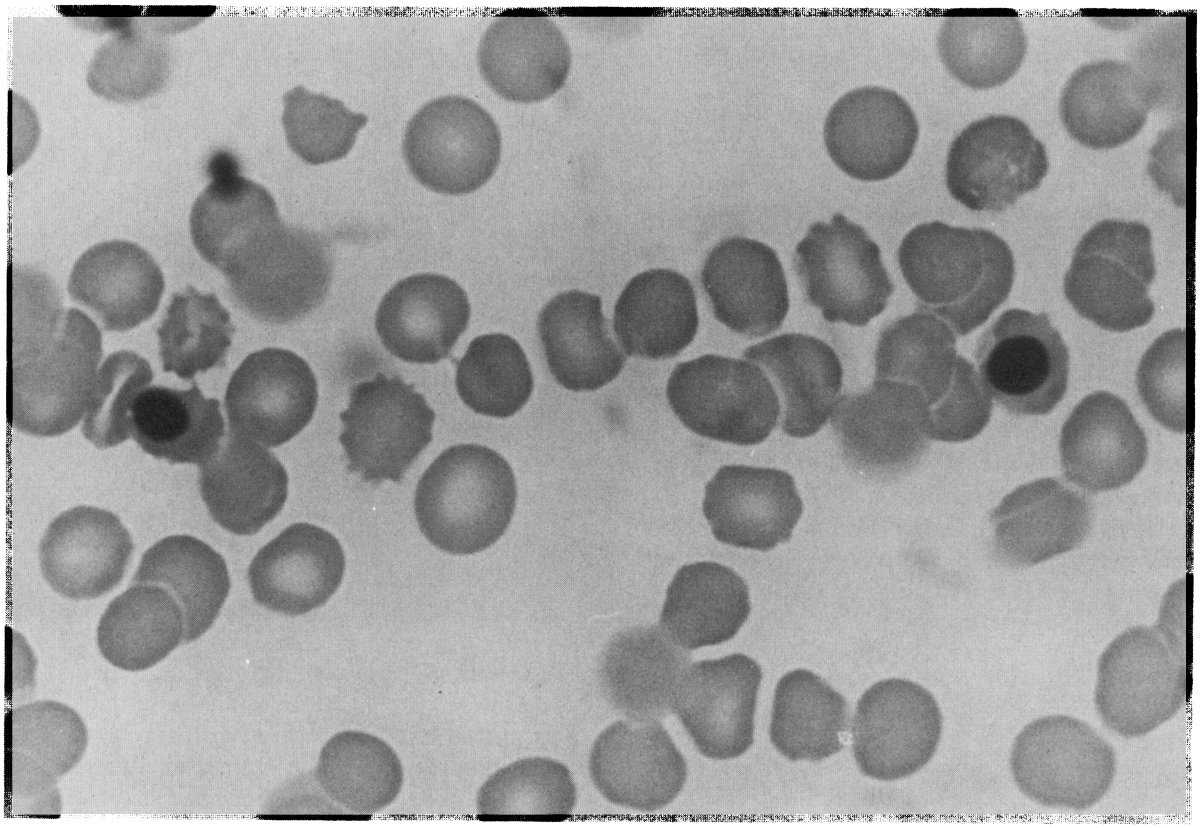

Figure 1.—Peripheral blood smear from the patient, showing several burr cells, nucleated red blood cells and schistocytes. (Reduced from magnification ×100.)

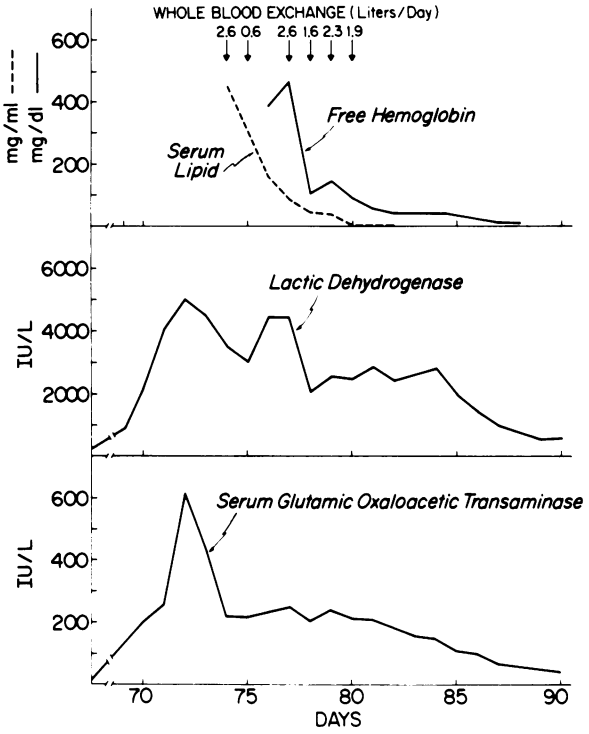

Figure 2.—The effect of whole blood exchange on serum lipid, free hemoglobin, lactic dehydrogenase and SGOT levels in a 25-year-old patient with fat-overload syndrome.

On day 74 whole blood exchanges were started to decrease the lipid and free hemoglobin and to remove damaged red cells (Figure 2). Ongoing hemolysis was detectable in the plasma until day 87.

By day 87 the plasma free hemoglobin had dropped to normal and the LDH was 1,119 IU per liter. There was pronounced improvement in pulmonary function. His renal function had not improved, however, and dialysis was begun on day 86. The patient died on day 99 of disseminated aspergillosis and graft-versus-host disease.

Discussion

Total parenteral nutrition has become an accepted means of treating the nutritional problems of patients unable to meet their caloric demands by oral intake.[3] Marrow transplant recipients represent a group of patients in whom hyperalimentation is particularly helpful and often crucial in their care. Persistent anorexia develops in many of these patients following chemoradiotherapy. Mucositis develops in others, with or without herpes stomatitis, preventing them from ingesting adequate calories. Still others, those with severe graft-versus-host disease of the gut, are unable to absorb enough calories to maintain their body mass. Many of these patients have notably increased metabolic demands either from infection, bleeding or other complications, thus making nutrition even more important.

We routinely administer total parenteral nutrition to all transplant recipients. This has been facilitated through the use of a large-bore right atrial catheter.[1] Using this technique, we have been able to substantially improve the nutrition of patients undergoing marrow transplantation.

Patients placed on total parenteral nutrition receive a crystalline amino acid solution with varying concentrations of dextrose depending on their caloric needs. In addition, we have used infusions of a 10 percent soybean oil emulsion as a means of providing additional calories and of preventing free fatty acid deficiency.[4,5] This substance has been well tolerated by most patients in most clinical settings, including ours. Surveys of patients receiving lipid emulsion therapy have supported its safety and efficacy as a means of providing isoosmotic calories.[6]

Attempts to administer free fatty acids to patients date back to the introduction of various vegetable oil preparations. The early preparations were associated with severe toxicity, including hyperpyrexia, embolic phenomena and renal failure. Soybean oil emulsions were introduced in 1935[7] as a means of supplementing amino acid solutions in protein-sparing therapy. These substances provided advantages over standard hyperalimentation solutions in that they were isoosmotic and could thus be given through a peripheral vein. They have high caloric content per unit volume and, when given in addition to amino acid solutions, provide a balanced nutritional program. In addition, administration of lipid emulsions was a means of preventing essential fatty acid deficiency, a syndrome described in patients receiving only amino acid solutions.[8,9] In contrast to their predecessors, the newer lipid preparations were associated with only minimal toxicity.

Sporadic reports have indicated that lipid emulsions affect a variety of organ systems. Several studies have shown that lipids given in this manner can depress T cell function.[10] One author reported increased platelet adhesiveness following lipid emulsion administration.[11] Animal studies have suggested that 10 percent intravenous fat emulsions have been associated with pulmonary hypertension and arterial hypoxemia.[12] A recent

report has shown decreased phagocytosis by macrophages when pretreated with a lipid preparation.[13]

A report of a lipid-overload syndrome was published by Belin and colleagues in 1976.[14] They described a patient in whom hypoxemia, oliguria, liver function abnormalities and coagulation defects developed following the infusion of a lipid emulsion. The syndrome resolved after cessation of lipid therapy.

Marks and co-workers[15] have recently described three cases of anemia and reticulocytosis in patients receiving lipid emulsions. These patients were also noted to have transient liver function abnormalities but did not experience renal or pulmonary dysfunction. In each case, the syndrome resolved without additional therapy following discontinuation of the lipid preparation.

Hessov and associates[16] have reported postmortem findings in three patients who had received lipid emulsions before they died. These patients displayed a pattern of fat deposition including large deposits in the heart, kidneys and small blood vessels. Each had severe underlying disease contributing to death.

Thus, it seems that there are certain pathologic states that are associated with altered lipid tolerance. Studies of lipid clearance in liver disease and following trauma suggest that lipid clearance is actually increased, presumably due to increased demands. Patients with Gram-negative septicemia and renal failure, however, seem less able to clear lipid from their blood. In the case described by Belin and colleagues,[14] the patient tolerated the lipid infusion well for a long period of time, only to become acutely overloaded for reasons that are not clear.

These reports indicate that one of the difficulties with lipid administration in parenteral nutrition is the lack of accurate monitoring techniques. While periodic nephelometric measurements seem to provide relatively good correlation with lipid concentration in vitro, they often fail to give the same correlation in vivo.[17] Visual assessment of changes in turbidity suffer from observer variation even with experienced personnel. Monitoring of fatty acid levels is expensive and time consuming.

Of interest in the present case is the appearance of burr cells and hemolysis. A particularly abnormal osmotic fragility curve was also noted in this patient, suggesting a membrane defect. These findings cleared after the removal of plasma lipid.

One of the distressing aspects of this case is the suddenness with which the syndrome developed, despite relatively little change in the patient's clinical status. If one examines LDH levels as an indicator of hemolysis, this process actually began several days before the serum was noted to be lipemic, and at a time when the SGOT value was normal. This emphasizes the inadequacy of visual inspection of the serum as a means of evaluating lipid tolerance.

The effectiveness of treatment of the syndrome remains discouraging. In the present case, whole blood exchange was undertaken in an attempt to remove lipid. Despite aggressive exchanges, however, the patient still required more than a week to clear his plasma entirely. This time course correlates reasonably well with that described by Belin and co-workers in the patient whose blood was not exchanged.[14] While the lipid load in our patient may have been greater than that described by Belin, his slow clearance may have simply resulted from the relative inaccessibility of the lipid-to-plasma clearing techniques.

After clearing of the patient's serum of lipid, the results of liver function studies, coagulation factors and peripheral blood smear showed improvement. But the renal failure persisted and may have been an irreversible consequence of the hemolytic episode.

While lipid emulsions seem to provide an appealing addition to the hyperalimentation program, like any intravenous therapy they are not without adverse effects. The lack of an accurate and readily available means of monitoring tolerance in critically ill patients remains a problem.

Summary

A fat-overload syndrome developed from infusion of 10 percent soybean emulsion in a 25-year-old patient who had a marrow transplant for aplastic anemia. This condition resulted in hyperlipidemia, respiratory distress, hemolytic anemia and acute renal failure. These events complicated an already complex posttransplant course. All the signs and symptoms except the acute renal failure reversed after whole blood exchange. The patient died of disseminated aspergillosis complicated by severe graft-versus-host disease.

REFERENCES

1. Hickman RO, Buckner CD, Clift RA, et al: A modified right atrial catheter for access to the venous system in marrow transplant recipients. Surg Gynecol Obstet 1979 Jun; 148:871-875

2. Storb R, Thomas ED, Weiden PL, et al: Aplastic anemia treated by allogeneic bone marrow transplantation: A report on 49 new cases from Seattle. Blood 1976 Dec; 48:817-841

3. Ota DM, Imbembo AL, Zuidema GD: Total parenteral nutrition. Surgery 1978 May; 83:503-520

4 Goodgame JT, Lowry SF, Brennan MF: Essential fatty acid deficiency in total parenteral nutrition: Time course of development and suggestions for therapy. Surgery 1978 Aug; 84:271-277

5. Wene JD, Conner WE, DenBesten L: The development of essential fatty acid deficiency in healthy men fed fat-free diets intravenously and orally. J Clin Invest 1975; 56:127-134

6. Hallberg D, Holm I, Obel AL: Fat emulsions for complete intravenous nutrition. Postgrad Med J 1967; 43:307-316

7. Holt E, Tidwell HD, McNair S: The intravenous administration of fat: A practical therapeutic procedure. J Pediatr 1935; 6:151-160

8. O'Neill JA Jr, Caldwell MD, Meng HC: Essential fatty acid deficiency in surgical patients. Ann Surg 1977; 185:535-542

9. Jeejeebhoy KN, Zohrab WJ, Langer B, et al: Total parenteral nutrition at home for 23 months, without complication, and with good rehabilitation—A study of technical and metabolic features. Gastroenterology 1973 Nov; 65:811-820

10. Mertin J, Hunt R: Influence of polyunsaturated fatty acids on survival of skin allografts and tumor incidence in mice. Proc Natl Acad Sci USA 1976 Mar; 73:928-931

11. Cronberg S, Nilsson IM: Coagulation studies after administration of fat emulsion, intralipid. Thromb Diath Haemorrh 1967; 18:664-669

12. McKeen CR, Brigham KL, Bowers RE, et al: Pulmonary vascular effects of fat emulsion infusion in unanesthetized sheep —Prevention by indomethacin. J Clin Invest 1978 May; 61:1291-1297

13. Strunk RC, Payne CM, Nagle RB, et al: Alteration of the structure and function of guinea pig peritoneal macrophages by a soybean oil emulsion. Am J Pathol 1979 Sep; 96:753-770

14. Belin RP, Bivins BA, Jona JZ, et al: Fat overload with a 10% soybean oil emulsion. Arch Surg 1976 Dec; 111:1391-1393

15. Marks LM, Patel N, Kurtides ES: Hematologic abnormalities associated with intravenous lipid therapy. Am J Gastroenterol 1980; 73:490-495

16. Hessov I, Melsen F, Haug A: Postmortem findings in three patients treated with intravenous fat emulsions. Arch Surg 1979 Jan; 114:66-68

17. Schreiner RL, Glick MR, Nordschow CD, et al: An evaluation of methods to monitor infants receiving intravenous lipids. J Pediatr 1979 Feb; 94:197-200

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Achromobacter Pneumonia

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PNEUMONIA IS ONE of the illnesses most frequently resulting in hospital admission. Yet, the specific cause of this common clinical condition is often difficult to determine, especially in small community hospitals where the laboratory experience and materials may be limited. Sensitivity profiles may, however, provide clues to the diagnosis and successful treatment of pneumonia.

Achromobacter xylosoxidans, first identified by Yabuuchi and Oyama[1] in 1971, is a Gram-negative bacillus and may be confused with *Pseudomonas* organisms. In fact, their sensitivity profiles may be quite similar, with the notable exception of their differing sensitivities to sulfa drugs. Recognition of *Achromobacter*'s characteristic sensitivity profile may help distinguish these two very similar organisms.

TABLE 1.—*Sensitivity of* Achromobacter xylosoxidans

Antimicrobial Drugs	*Sensitivity*
Amikacin	R
Ampicillin	R
Carbenicillin	S
Cefamandole	I
Cephalothin	R
Chloramphenicol	R
Clindamycin	R
Erythromycin	R
Gantrisin	S
Gentamicin	I
Kanamycin	R
Oxacillin	R
Penicillin	R
Trimethoprim/sulfamethoxazole (Septra)	S
Tetracycline	R
Tobramycin	I
Vancomycin	R

R = Resistant I = Intermediate S = Sensitive

Report of a Case

A 71-year-old woman who had never smoked was seen with a three-day history of fever, cough and anorexia. There was production of between 2 and 3 oz of thick, grayish brown sputum per day. There was a documented weight loss of 18 kg (40 lbs) over the past two years. There were at least ten previous episodes of pneumonia, several occurring in childhood. An extensive workup for weight loss and possible malignancy had been conducted previously, with completely negative findings on all testing, including cultures and cytology of sputum for tuberculosis, a body scan and α_1-antitrypsin immunology test. Other medical problems included a benign cyst of the maxillary sinus plus hiatus hernia with reflux and esophagitis controlled with cimetidine.

On admission the patient was noted to be pale, febrile and dyspneic at rest. Moist rales were heard in the left lung field. X-ray studies of the chest showed two infiltrations on the right side. Leukocytes numbered 9,100 per cu mm and determination of arterial blood gases revealed moderate hypoxemia. The electrocardiogram was interpreted as showing right axis deviation, P pulmonale and low voltage, suggesting chronic pulmonary disease. Pulmonary function tests showed severely re-

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